

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 27867		Date of mailing (day/month/year) 26 JAN 2005 FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/IL04/00305	International filing date (day/month/year) 01 April 2004 (01.04.2004)	Priority date (day/month/year) 04 April 2003 (04.04.2003)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): G01N 33/53 and US Cl.: 435/7.1, 7.21, 7.7, 7.9, 40.5, 40.51, 40.52			
Applicant BIOVIEW LTD			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

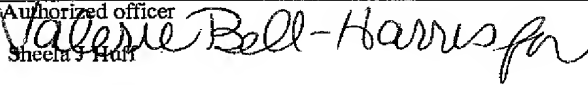
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer  Telephone No. (571) 272-1600
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/IL04/00305

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
- a. type of material
- ☐ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material
- ☐ in written format
- ☐ in computer readable form
- c. time of filing/furnishing
- ☐ contained in international application as filed.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IL04/00305

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>6,9,14-18,24,26-27,29-30,32-71</u>	YES
	Claims <u>1-5,7-8,10-13,19-23,25,28,31</u>	NO
Inventive step (IS)	Claims <u>6,9,14-15,17-18,24,26-27,29,30,32-71</u>	YES
	Claims <u>1-5, 7-8,10-13,16,19-23,25,28,31</u>	NO
Industrial applicability (IA)	Claims <u>1-71</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-5, 7, 10-13, 19-23, 25, 28 and 31 lack novelty under PCT Article 33(2) as being anticipated by McCORMICK et al.

This reference describes the assessment of HER2 using two different stains (immunohistochemical and fluorescence in situ hybridization). The analysis was done in formalin-fixed, paraffin-embedded breast tumors.

Claims 1-5, 8, 19-23 and 25 lack novelty under PCT Article 33(2) as being anticipated by VAN AGTHOVAN et al.

This reference describes the assessment of malignant breast tissues using dual staining immunohistochemistry.

Claims 1-7, 10, 13, 16, 19-23, 25, 28 and 31 lack an inventive step under PCT Article 33(3) as being obvious over BEUG et al.

This reference describes the use of histochemical staining with anti-TGFBeta antibodies and the determination of mRNA level using in situ hybridization in tumor cells.

The only difference between the reference and the instant invention is that the reference did not show use the assays.

In view of the suggestion in the reference, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to use the suggested assays to determine the production of TGFBeta1 in tumor cells.

Claims 1-5, 7, 11, 13, 19-23, 25 and 31 lack novelty under PCT Article 33(2) as being anticipated by HENNING et al.

This reference describes the use of cytochemical and histochemical staining to determine molecular markers for tumors in uterine cervical smears. The assays were detected using chromogenic or fluorescent detection. The examples describes the use of an antibody and DNA probe or the use of two antibodies.

Claims 1-71 meet the criteria set out in PCT Article 33(4), and thus the industrial applicability because the subject matter claimed can be made or used in industry.

Claims 6, 9, 14-15, 17-18, 24, 26, 27, 29, 30 and 32-71 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed invention.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.